REMARKS/ARGUMENTS

The claims are 2 and 4-9. Claim 9 has been amended to better define the invention and to incorporate the subject matter of claim 3. Accordingly, claim 3 has been canceled. In addition, the specification has been amended to correct a clerical error in the formula at page 17, thereby conforming the formula to the original text of the published PCT application. Support for the claims may be found, *inter alia*, in the disclosure at page 9. Reconsideration is expressly requested.

The Examiner refused to grant Applicant's request for foreign priority on the basis of German Priority Application No. 103 52 692.7 because a certified English translation of this application had not been filed. In response, Applicant submits herewith an English translation of German Priority Application No. 103 52 692.7 filed November 12, 2003 as requested by the Examiner as well as a statement that the translation is accurate.

Claim 9, with dependent claims 2-5 and 7-8, were rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the use of the term "chemically modified" in claim 9. In response, Applicant has amended claim 9 to introduce the subject matter as disclosed at page 9 of the disclosure and to incorporate the

subject matter of claim 3. Thus, claim 9 now specifies that the aqueous hypo-oncotic solution includes, *inter alia*, high molecular weight intermolecularly crosslinked hyperpolymeric hemoglobin, which is further chemically modified by covalant linkage of reactive effectors or covalent linkage of other macromolecules selected from the group consisting of poly(ethylene oxides), poly(ethylene glycols), dextranes, and hydroxyethylstarches. It is respectfully submitted that the foregoing amendment overcomes the Examiner's rejection to the claims under 35 U.S.C. 112, second paragraph, and Applicant respectfully requests that the rejection on that basis be withdrawn.

Claims 2-9 were rejected under 35 U.S.C. 103(a) as being unpatentable over *Nho et al. U.S. Patent No. 5,234,903* and *Winslow U.S. Patent No. 6,432,918* in view of *Grinstaff et al. U.S. Patent No. 5,665,383*. Essentially, the Examiner's position was that *Nho et al.* discloses the method recited in the claims except for features which were said to be taught by *Winslow* and *Grinstaff et al.*

This rejection is respectfully traversed.

As set forth in claim 9 as amended, Applicant's invention provides a method of treating acute pulmonary edema including providing an aqueous hypo-oncotic solution including electrolytes and high molecular weight intermolecularly crosslinked hyperpolymeric hemoglobin, which is further chemically modified by covalent linkage of reactive effectors, or covalent linkage of other macromolecules selected from the group consisting of poly(ethylene oxides), poly(ethylene glycols), dextranes, and hydroxyethylstarches. The solution is administered to a person to treat acute pulmonary edema, wherein the solution before administration to a person has a (hypo) oncotic pressure below 5 mbar.

Surprisingly, Applicant has found that additive administration can be performed using its method because the coloidal-osmotic (=oncotic) pressure of the blood is raised only slightly and the blood volume is therefore hardly increased at all. The use and administration according to Applicant's amended claim 9 is thus almost volume-neutral based on the blood into which injection is performed. As a result, hyperpolymeric hemoglobin derivatives may be used therapeutically for the first time as a blood additive for the treatment of pulmonary edema.

The Examiner has generally rejected the claims by asserting

that "Each of the references teaches introvascular administration of aqueous hypooncotic solutions, below 28 mmHg.... See page 5, lines 13 ff of the Office Action; however, the Examiner has provided no actual citation supporting that statement. On the contrary, as discussed below, it is respectfully submitted that the state of the art teaches the contrary. It should be noted that Applicant's invention as recited in claim 9, as amended, provides a method of treating acute pulmonary edema including providing an aqueous hypo-oncotic solution including electrolytes and high molecular weight crosslinked hyperpolymeric hemoglobin further chemically modified and administering the solution to a patient in need thereof whereby the solution has an oncotic pressure of below 5 mm Hg.

Thus the decisive features are:

i) the hypo-oncotic solution (below 5 mm Hg); to be administered in case of pulmonary edema; and

ii) the high molecular weight crosslinked hyperpolymeric hemoglobin further modified by covalent linkages as recited in Applicant's claim 9 as amended.

Page 3, second full paragraph, and page 4, first and second full paragraphs of Applicant's disclosure, discusses the state of

the art. There it is pointed out that all plasma expanders (plasma expander solutions) -- including oxygen carrying plasma expanders (= 'blood substitutes') -- when being designated to be useful as agents to replace blood, have to be nearly iso-oncotic (or even hyper-oncotic). Thereby, normal (iso) oncotic pressure of human blood plasma is about 25 mm Hg. See e.g. http://physioweb.med.uvm.edu/bodyfluids/isf-plas.htm.

The primary reference to *Nho et al. expressis verbis* teaches the use of blood substitutes (=oxygen transporting plasma expanders). See col. 8, lines 1-3 of *Nho et al.*: "*(iii) the PEG-bHb of the invention is stable, thereby permitting its clinical use as a blood cell substitute and volume expander; ....*".

Furthermore, Example V (columns 20 - 21) of *Nho et al.* teaches polymers (= polymeric or multimeric conjugates) consisting of hemoglobin and PEG (Polyethylenglycol, i.e. a macromolecule), which are still iso-oncotic as can be taken from Table IV, at column 21, lines 38-59 showing the values of the oncotic pressure ranging from 20 to 24 mmHg both for the five PEGylated hemoglobin derivatives according to *Nho et al.* as well as for the control (native hemoglobin).

Thus, contrary to the Examiner's position, it is respectfully submitted that *Nho et al.* **fails** to disclose or suggest the use of hypo-oncotic hemoglobins. Moreover, the *Nho et al.* agent is concerned with a hemoglobin chemically modified by covalent linkage to polyethylenglycol. See abstract or claims of *Nho et al.* Such modification is indeed also possible in the agent as used in Applicant's claim 9 as amended; however, besides the covalent linkage present, Applicant's agent is also cross-linked to a high degree and therefore hyperpolymer while the *Nho et al.* hemoglobin is not.

The same is true regarding the *Winslow* reference. Like *Nho et al.*, *Winslow* teaches "blood substitutes", including oxygen-carrying and non-oxygen-carrying components, having a normal oncotic pressure as can be taken for example from column 3, lines 26-49 of *Nho et al.*

The oncotic pressure of *Winslow et al.*'s compositions, which include mixtures of an oxygen-carrying component and a non-oxygen-carrying component should, as expressly stated by *Nho et al.*, be greater than that of plasma. See, for example, col. 3, lines 50 ff of *Winslow* wherein it is stated

> "More specifically, it is contemplated that the compositions of the present invention will contain one or more of the following properties: i) ...; ii) oncotic pressure higher than that of plasma; iii)...."

Contrary to this teaching of *Winslow*, the Examiner asserts at page 4, lines 10-11 of the Office Action that "*Specifically, Winslow teaches an oncotic pressure of less than 28 mmHg (paragraph 30)*". First of all, it is unclear what the Examiner is referring to by paragraph 30 of *Winslow*. Moreover, no such value can be located in *Winslow* that does not include a hypo-oncotic solution, because the normal value of about 25 mm Hg is also "less than 28 mmHg", and is still iso-oncotic and not hypo-oncotic. Therefore, it is respectfully submitted that the Examiner's determination of the scope and content of the *Winslow* patent is in error.

Grinstaff et al. teaches a method of producing hollow microparticles with a polymeric shell, e.g. made of insoluble crosslinked hemoglobin. These particles are to be used as carriers for biological agents to be delivered into the body; however, an insoluble hemoglobin cannot be considered as a suggestion for the administration as currently recited in claim

9, as amended, because in Applicant's method a solution is administered. Consequently the agent (hemoglobin derivative) has to be soluble or else no solution thereof would be possible. Accordingly, it is respectfully submitted that the relevance of *Grinstaff et al.* is doubtful.

As pointed out previously, Applicant's method as recited in claim 9, as amended, is concerned with the treatment of lung edema using a crosslinked modified hemoglobin, the oncotic pressure of a solution thereof being much less than that of blood, especially less than 5 mm Hg. As pointed out in the paragraph bridging pages 7-8 of the disclosure relating to the Detailed Description of the Invention, acute pulmonary edema can be treated efficiently "by administering an aqueous solution of hyperpolymeric hemoglobin derivatives that can be added to the blood, whose oncotic pressure in aqueous <u>is much lower</u> than that of the existing blood and thus shows a hypo-oncotic pressure as an additive". Furthermore, page 12, first full paragraph of Applicant's disclosure states "It has been found in particular that the mentioned hyperpolymers are suitable when their degree of polymerization is high enough for the oncotic pressure of solutions to be below 5 mbar with the therapeutic concentration of the chemically modified high molecular weight crosslinked

hemoglobins in an aqueous medium...." (which is less than about 15% of the oncotic pressure of human blood plasma).

It is respectfully submitted that claim 9, as amended, clearly sets forth the subject matter of Applicant's method so as to distinguish over the prior art cited by the Examiner. As pointed out above, none of the cited references discloses or suggests such a low pressure in solutions comprising oxygen carriers. On the contrary, the state of the art teaches the use of compositions exhibiting the commonly known and applied oncotic pressure, as noted above.

In view of the differences pointed out, it is respectfully submitted that the Examiner's position that "It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of *Nho et al., Winslow and Grindstaff et al.* to achieve the invention as claimed" (see page 5, line 11-13 of the Office Action) is incorrect.

Nho et al. and *Winslow* teach the use of blood substitutes, and liquids for infusion which can replace missing blood, lost due to injuries (by accident or war) or during surgery, in acute situations, related to anemia, hypovolemia, shock, "requiring

massive transfusion." See, e.g., col. 17, lines 43-56 of *Nho et al.* As pointed out, such agents are about iso-oncotic. Moreover, there is no disclosure or suggestion in *Nho et al.* to the use of such agents to treat lung edema.

Essentially, the Examiner has rejected all claims in view of the state of the art suggesting specific hemoglobins and their general usefulness; however, it should be noted that in Applicant's claims, no agent itself is claimed per se, but rather a specific method of treatment, which method is completely different from that suggested in the art. Although the art suggests to administer the blood substitute to a person in need thereof in view of a lack of blood/oxygen (see *Nho et al.*), it will be expected that in such case the administration of oncotic solutions are necessary to avoid further decrease of blood pressure. Thus, the aim of *Nho et al.* can be considered as to augment blood pressure which will certainly not be achieved with the administration of a hypo-oncotic oxygen-carrying blood additive into existing blood according to Applicant's method as recited in claim 9 as amended because with Applicant's method one can change the oncotic pressure and consecutively the volume of the blood only to a minor/marginal extent.

The same applies to *Winslow* which explicitly suggests the use of iso-oncotic or hyper oncotic solutions.

Consequently it is respectfully submitted that it would not be possible for a person skilled in the art to have a "reasonable expectation of success and motivation" to achieve Applicant's method as recited in claim 9 as amended, where not even one of the decisive elements of the claimed elements i), ii) as explained above is suggested in the art. Accordingly, it is respectfully submitted that claim 9 as amended, together with claims 2 and 4-8, which depend thereon, contain patentable and unobvious subject matter.

Claims 2-9 were also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-16 of U.S. Patent No. 6,956,025 or claims 15-17 of U.S. Patent No. 7,005,414. Essentially, the Examiner's position was that claims 2-9 are not patentablity distinct from the specified claims of the '025 or the '414 patents because both sets of claims recite methods of treating patents in need thereof with crosslinked hemoglobin intravascularly in a physiologically compatible solution and neither the '025 nor the '414 patent claims specifically exclude

a hemoglobin derivative which is crosslinked and in a multimer configuration.

This rejection is respectfully traversed.

The Examiner has argued that the '025 and the '414 patent claims relate to hemoglobin and methods of treating patients with such hemoglobin which according to claim 1 of the '025 patent and claim 13 of the '414 patent is crosslinked and not excluded; however, it should be noted that Applicant's invention as recited in claims 2-9 does not claim hemoglobin or a process for the production, but rather a specific application thereof, namely the treatment of pulmonary edema. This specific use/method of treatment is different from the use/method of treatment of the '025 and '414 patent claims.

Moreover, the manner of use/treatment itself is different insofar as Applicant's claims 2-9 recite that the hemoglobin is used as hypo-oncotic solution which is neither disclosed nor suggested by the '414 and '025 patent claims. In claims 14-15 of the '414 patent and claims 15-17 of the '025 patent, hemoglobin is used an as artificial oxygen carrier as blood substitute, an additive in patients in need thereof.

Applicant's invention as recited in claims 2-9 relates to a method of treating acute pulmonary edema, which is an abnormal fluid accumulation in the intracellular space treated prior to Applicant's invention symptomatically, e.g. by corticoids, respiratory air, and therapy for cardiac insufficiency. (See Applicant's disclosure at page 6).

Thus, according to the '414 and the '025 patent claims, patients are treated who are in need of substitutes or additives for blood. In contrast, according to Applicant's method as recited in claims 2-9, patients are treated who are not in need of blood substitutes/additives, but rather who are in need of management of the abnormal fluid accumulation as discussed above.

Accordingly, it is respectfully submitted that claims 14-16 of the '025 patent and claims 15-17 of the '414 patent fail to disclose or suggest the treatment that is recited in Applicant's claims 2-9. Therefore, it is respectfully submitted that claims 2-9 are patentably distinct from the cited patent claims because there is no claim related to an oxygen carrier per se, but rather to a use thereof. Prior to Applicant's invention, the oxygen carriers of the '414 and the '025 patent claims had not been used to treat pulmonary edema because such treatment is unrelated to

the administration as blood additive or substitute. In addition, the specific administrative modus (hypo-oncotic solution) of claim 2-9 is nowhere disclosed or suggested in the '414 and '025 patent claims.

In summary, claim 9 has been amended and claim 3 has been canceled. The specification has also been amended. In view of the foregoing, it is respectfully requested that the claims be allowed and that this case be passed to issue.

Respectfully submitted,

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Enclosure: Copy of Petition - 1 month extension of time
Certified Translation of DE 103 52 692

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on October 23, 2008.

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